27. (New) The production process according to claim 1, wherein R of the general formulas 3, 4 and 5 represents a trifluoromethyl group.

28. (New) The production process according to claim 1, wherein R of the general formulas 3, 4 and 5 represents a fluorine atom.

C5

REMARKS

Favorable consideration and allowance are respectfully requested for claims 1-13 and 25-28 in view of the foregoing amendments and the following remarks.

New claims 25-28 are submitted herewith and relate to hydrogenolysis temperatures (see, e.g., Examples 9, 12, 15, 18, and 21 on pages 42, 45-46, 48-49, 51-52, 54-55, respectively) and substituted groups and atoms for various formulas (see, e.g., claim 1). No new matter has been added.

In the Office Action dated May 3, 2002, the oath or declaration was found defective; claims 1, 5, 8, and 10 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite; claims 1-9 and 12 were rejected under 35 U.S.C. § 103(a) as being unpatentable over German disclosure DE 38 19 438 ("Bringman") in view of U.S. Patent No. 6,211,244 ("Van Wagenen"); and claims 10, 11, and 13 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Japan Patent No. 9-278718 ("Hagitani"). These rejections are respectfully traversed.

Claims 1, 5-8, 10, 12, and 13 have been amended, claims 14-24 have been previously cancelled, and claims 25-28 have been added; thus, claims 1-13 and 25-28 are pending in this application.

Oath/Declaration

The declaration was found defective because "it does not identify the mailing or post office address of each inventor." The information referenced by the Examiner is set forth in the Application Data Sheet that was filed with the filing papers submitted on May 11, 2001. Withdrawal of the objection is requested.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1, 5, 8, and 10 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the use of parentheses and "chemical #" referencing the specification. Such parentheses and chemical numbering have been removed from the claims. As such, withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 103(a)

Claims 1-9 and 12 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Bringman in view of Van Wagenen. At best, Bringman discloses a fluorine substituent at the ortho-position on the phenyl group. According to the claimed invention, R of the phenyl group of the general formulas [3], [4] and [5] represents a fluorine atom or trifluoromethyl group where the fluorine atom is

defined as being not at the ortho position when R is a fluorine atom and n is 1. In other words, claim 1 recites that a single fluorine atom is at the meta or para-position on the phenyl group, which is clearly different from Bringman's disclosed fluorine atom at the ortho-position. Moreover, the claimed trifluoromethyl group (R) of the claimed invention is not disclosed nor suggested by Bringman.

Applicants unexpectedly found that the position-selective hydrogenolysis of the claimed substrate (i.e., the optically active secondary amine of the general formula [4]), in which R is a fluorine atom (of meta- or para-position when n is 1) or trifluoromethyl group, proceeds efficiently to produce the target product (i.e., the optically active 1-(fluoro- or trifluoromethyl-substituted phenyl)ethylamine of the general formula [5]). Therefore, the claimed hydrogenolysis is not obvious over the disclosure of Bringman as is further discussed below.

The positional selectivity of the hydrogenolysis is governed by the electronic effect and the steric effect of a substituent(s) on the phenyl group. First, the electronic effect is demonstrated as Bringman's substitutents of Ar, which are disclosed in Beispiel Nr. 1-9 on page 5 of Bringman, are strongly electron-donating groups, and those (i.e., fluorine and chlorine), which are disclosed in Beispiel Nr. 10-11, are weakly electron-attractive groups. In other words, strongly electron-attracting groups (such as trifluoromethyl group of the claimed invention) are not disclosed nor suggested as the substitutents of Ar in Beispiel Nr. 1-11 of Bringman. It is known that a strongly electron-attracting group on an aromatic ring strongly reduces the electron density of the aromatic ring. Importantly, Bringman states at

page 4, lines 18-20, that the compound of the general formula I is predominantly formed if the substituent has the function of increasing the electron density of the aromatic ring (Ar), and, in contrast, the decomposition selectivity from the compound of the general formula II to the compound of the general formula I is reduced if the substitutent does not have such a function. Bringman's statement means that the position-selective hydrogenolysis from the compound of the general formula II to the compound of the general formula I does not proceed successfully, where the substitutent of the aromatic ring is a strongly electron-attracting group. In contrast with Bringman, Applicants unexpectedly found that the claimed position-selective hydrogenolysis proceeds successfully by specifically selecting a strongly electron-attracting group, such as a trifluoromethyl group, as R in the general formula [4] in the claimed invention.

Secondly, the steric effect is explained below. The ortho-positioned fluorine is disclosed as the substitutent of Ar in Bringman (see page 5, Beispiel Nr. 10). Because the ortho-position is closer to the breakage position (i.e., the position between nitrogen atom (N) and the chiral carbon (C*) bonded to Phenyl in formula II of Bringman) in the hydrogenolysis than the meta- and para-positions, it is understood that the steric effect in the hydrogenolysis becomes the greatest by the ortho-positioned substituent. In other words, a person skilled in the art would not expect that the position-selective hydrogenolysis proceeds successfully by using a substrate in which a meta- or para-position fluorine atom is a substitutent of the phenyl group.

Thus, the position-selective hydrogenolysis of the claimed invention is clearly not obvious over the disclosure of Bringman with respect to both the electronic effect and the steric effect. In other words, Applicants unexpectedly found that a position-selective hydrogenolysis proceeds successfully even by using the claimed substrate (i.e., the optically active secondary amine of the general formula [4]), in which R is fluorine atom or trifluoromethyl group, except for the ortho position when R is a fluorine atom and n is 1.

Van Wagenen does not cure the deficiencies of Bringman. Van Wagenen discloses a compound having STRUCTURE III (see column 5, lines 4-10), which is related to the claimed secondary amine of the general formula [4]. However, as far as a structure of bis(1-arylethyl)amine, which is the important basic structure of the claimed secondary amine of the general formula [4], is concerned, Van Wagenen discloses only hydrogen, alkoxy group, alkyl group, chlorine, and fluorine as the substituents (see, e.g., formulas 17K to 17P in Fig. 11 on sheet 12). Thus, a trifluoromethyl group of the claimed invention is not specifically disclosed in Van Wagenen as a substitutent of the phenyl group. Regarding fluorine, Van Wagenen discloses compound No. 17O (see Fig. 11 on sheet 12) having a structure of bis(1-arylethyl) amine and a meta-positioned fluorine on the phenyl group. However, this compound No. 17O of Van Wagenen contains another substitutent—a methoxy group (H_3CO-) on the phenyl group. This methoxy group is excluded from R of the general formula [4] of the claimed invention. Therefore, the compound No. 17O of Van Wagenen is substantially different from the secondary amine of the general

formula [4] of the claimed invention. Thus, claim 1 and its dependent claims are not obvious over the combined teachings of Bringman and Van Wagenen and should be allowed. Accordingly, withdrawal of the rejection of claims 1-9 and 12 is respectfully requested.

The patentability of several dependent claims will be discussed below.

Van Wagenen discloses a compound (see column 13, lines 15-20 and the formula on page 5 of the Office Action) such as the compound No. 17O (see Fig. 11 on sheet 12), which contains 1-naphthyl group. In contrast, Ar of the general formulas [3] and [4] of claim 26 is a phenyl group or 2-naphthyl group. Therefore, claim 26 should also be allowed for this additional, independent reason.

Regarding claims 4 and 25, Bringman discloses a hydrogenation at a reaction temperature of 0-50°C under a hydrogen pressure of 1-300 bar (i.e., 0.1-30 MPa) using a noble metal of the grup VIII of the periodic table (see page 3, lines 20-21), preferably at a reaction temperature of 20-50°C under a hydrogen pressure of 1-200 bar (i.e., 0.1-20 MPa) using palladium (see page 3, lines 62-63). According to Examples 1-11 of Bringman, the hydrogenation was actually conducted at 25°C under a hydrogen pressure of 180 bar (18MPa) using 2wt% of palladium (in terms of metallic palladium). Under these conditions, it is necessary to use a high-pressure reaction vessel and a large amount of palladium. Applicants unexpectedly found that it is possible to drastically reduce the hydrogen pressure and the amount of palladium as catalyst, as shown by the data of Table 1 on page 28, line 23 to page 29, line 7 of the specification. In other words, as recited in claim 4, it is possible to

carry out the hydrogenolysis successfully using a group VIII metal (e.g., palladium) catalyst at 0.5wt% or less (when converted as metal) in a hydrogen atmosphere of 2MPa (20bar) or lower, where the reaction temperature is 40°C or higher. Furthermore, according to claim 25, the hydrogenolysis is carried out while heating at 55°C or higher. This reaction temperature is clearly higher than the reaction temperature range (0-50°C) of Bringman. Thus, claims 4 and 25 should also be allowed for these additional, independent reasons.

Claim 2 is also independently patentable. Although Van Wagenen discloses that there is a reducing agent (i.e., sodium triacetoxyborohydride) suitable for synthesizing particular compounds (9R, 14U and 16P) (see column 30, lines 35-38) and discloses that sodium cyanoborohydride was used for reducing the intermediate imines to produce the compounds 8J, 8U, 11X, 17M and 25Y (see column 30, lines 42-47), these target compounds are substantially different from the claimed secondary amine of claimed general formula [4]. Applicants unexpectedly found that sodium borohydride is the best hydride reducing agent for asymmetrically reducing the imine of the formula [3] into the secondary amine of the formula [4] (see page 8, line 21 to page 9, line 9 of the specification). Therefore, claim 2 should also be allowed for this additional, independent reason.

Regarding claim 8, the Examiner asserts that Van Wagenen "teaches (Column 32, lines 20-38) that compounds of the general structure taught can be converted to the hydrochloride salt and recrystallized as a method of purification." Page 5, last line to page 6, line 2 of the Office Action. Applicants disagree. In

Example 9 of Van Wagenen, the free base, not hydrochloride salt, was recrystallized, and was turned into the hydrochloride salt only for measuring its melting point. Although Van Wagenen (column 36, lines 25-39) discloses in Example 17 that the free base (amine) was converted to its HCl salt, followed by recrystallization, the free base is substantially different from the claimed fluorine-containing substrate (i.e., the optically active secondary amine of the formula [4]). Because of this difference, a person skilled in the art would not expect that the claimed fluorine-containing substrate of claim 8 would be purified by recrystallization of its salt of an inorganic acid or organic acid, based on the disclosure of Van Wagenen. Therefore claim 8 and its dependent claims should be allowed for this additional, independent reason.

The specific acids of claim 9 that are to be combined with the optically active secondary amine of the formula [4] to produce its salt are not disclosed nor suggested by Van Wagenen. In fact, Applicants unexpectedly found that it is possible to efficiently purify the claimed secondary amine of the formula [4] by using the specific acids of claim 9. Therefore, claim 9 should also be allowed for this additional, independent reason.

Claims 10, 11, and 13 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Hagitani. The Examiner's assertion at page 6, lines 4-6, of the Office Action that, "[t]he instantly claimed invention ... recrystallization." is not correct. According to claim 10, the purification target is specifically limited to an optically active 1-(3,5-bis-trifluoromethylphenyl)ethylamine of the formula [6], not

racemic fluoro- and trifluoromethyl-substituted phenethylamines. Hagitani (see Machine translation, page 1, "SOLUTION"; and page 4, lines 7-9) discloses the use of a dialkyl ether (e.g., methyl-t-butyl ether (MTBE)) as a recrystallization solvent in a optical resolution of racemic mixture of a 1-phenethylamine of the formula with an optically active mandelic acid. This phenethylamine of Hagitani is not limited to a disubstituted one, but may be an unsubstituted phenethylamine, a monosubstituted phenethylamine or disubstituted phenethylamine (see the definition of R^1 and R^2 in the formula). As above, a racemic mixture of a 1-phenethylamine is subjected to an optical resolution in Hagitani to obtain an optically active 1-phenethylamine, in contrast to the optically active 1-(3,5-bis-trifluoromthylphenyl)ethylamine that is purified according to the claimed invention. Thus, the claimed invention is substantially different from Hagitani's disclosure. Therefore, claim 10 and its dependent claims should be allowed. Accordingly, withdrawal of the rejection of claims 10, 11, and 13 is respectfully requested.

In view of the foregoing amendments and remarks, the application is respectfully submitted to be in condition for allowance, and prompt favorable action thereon is earnestly solicited.

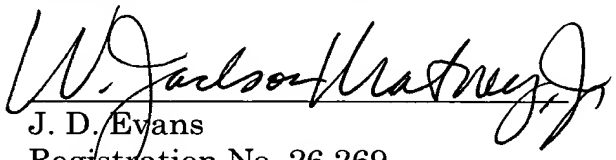
If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response; please

charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #3007/49966).

Respectfully submitted,

November 4, 2002



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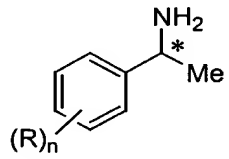
MARKED-UP VERSION TO SHOW CHANGES

IN THE CLAIMS

1. (Amended) A process for producing an optically active 1-(fluoro- or trifluoromethyl-substituted phenyl)ethylamine represented by the general formula 5 [[5]]:

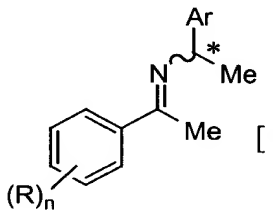
[[Chemical 3]]



[5]

[()wherein, R represents a fluorine atom or trifluoromethyl group, n represents 1 to 5, and it takes an arbitrary substitution position, except for the ortho position when R is a fluorine atom and n is 1, and the asterisk [(*)] represents a chiral carbon()], by asymmetrically reducing an optically active imine represented by the general formula 3 [[3]]:

[[Chemical 1]]

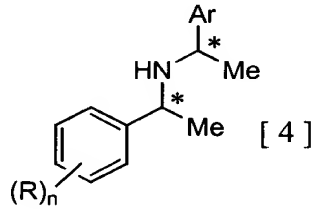


[3]

[()wherein, R represents a fluorine atom or trifluoromethyl group, n represents 1 to 5 and it takes an arbitary substitution position, except for the ortho position when R is a fluorine atom and n is 1, Ar represents a phenyl group or 1- or 2-naphthyl group, and the asterisk [(*)] represents a chiral carbon()], using a hydride reducing

agent, converting to an optically active secondary amine represented by the general formula 4 [[4]]:

[[Chemical 2]]

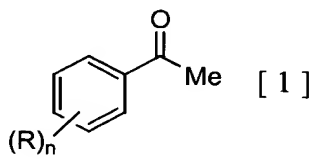


[4]

[()wherein, R represents a fluorine atom or trifluoromethyl group, n represents 1 to 5 and it takes an arbitrary substitution position, except for the ortho position when R is a fluorine atom and n is 1, Ar represents a phenyl group or 1- or 2-naphthyl group, and the asterisks [(*)] represent chiral carbons[)], and subjecting the secondary amine, its salt of an inorganic acid or its salt of an organic acid to hydrogenolysis.

5. (Amended) The production process according to claim 1, wherein the optically active imine represented by the general formula 3 [[3]] is an optically active imine obtained by dehydration and condensation under acidic conditions of a fluoro- or trifluoromethyl-substituted phenylmethyl ketone represented by the general formula 1 [[1]]:

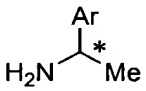
[[Chemical 4]]



[1]

[(]wherein, R represents a fluorine atom or trifluoromethyl group, n represents 1 to 5, and it takes an arbitrary substitution position, except for the ortho position when R is a fluorine atom and n is 1[)], and an optically active primary amine represented by the general formula 2 [[2]]:

[[Chemical 5]]



[2]

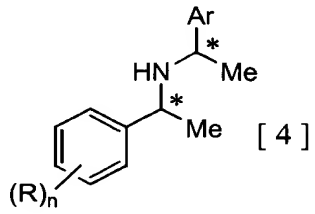
[(]wherein, Ar represents a phenyl group or 1- or 2-naphthyl group, and the asterisk [(*)] represents a chiral carbon[)].

6. (Amended) The production process according to claim 1, wherein stereochemistry of the compound represented by the general formula 3, 4 or 5 [[3], [4] or [5]] is R form or S form.

7. (Amended) The production process according to claim 5, wherein stereochemistry of the compound represented by the general formula 2 [[2]] is R form or S form.

8. (Amended) A purification process, characterized in that an optically active secondary amine represented by the general formula 4 [[4]]:

[[Chemical 6]]

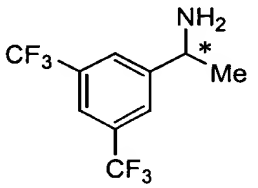


[4]

[()wherein, R represents a fluorine atom or trifluoromethyl group, n represents 1 to 5 and it takes an arbitrary substitution position, except for the ortho position when R is a fluorine atom and n is 1, Ar represents a phenyl group or 1- or 2-naphthyl group, and the asterisks [(*)] represent chiral carbons[)] is converted to a salt of an inorganic acid or organic acid, followed by purification by recrystallization.

10. (Amended) A purification process, characterized in that an optically active 1-(3,5-bis-trifluoromethylphenyl)ethylamine represented by the formula 6 [[6]]:

[[Chemical 7]]



[6]

[()wherein, the asterisk [(*)] represents a chiral carbon[)], is converted to a salt of an inorganic acid or organic acid, followed by purification by recrystallization.

12. (Amended) The purification process according to claim 8, wherein stereochemistry of the compound represented by the general formula 4 [[4]] is R form or S form.

13. (Amended) The purification process according to claim 10, wherein stereochemistry of the compound represented by the formula 6 [[6]] is R form or S form.